Sex-specific Effects of Asthma on Pulmonary Function in Children

KIROS BERHANE, ROB McCONNELL, FRANK GILLILAND, TALAT ISLAM, W. JAMES GAUDERMAN, EDWARD AVOL, STEPHANIE J. LONDON, ED RAPPAPORT, HELENE G. MARGOLIS, and JOHN M. PETERS

Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California; National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina; and California Air Resources Board, Sacramento, California

To evaluate the effects on lung function of asthma, time since diagnosis of asthma, and age at diagnosis of asthma, we examined school children in a cohort of 2,277 fourth- and seventh-graders at least twice during a 4-yr follow-up period. Sex-specific models for each lung function were fitted through mixed-effects models that used regression splines and captured age-dependent trends in the effect of asthma on lung function. In males, a history of asthma was associated with large and statistically significant deficits in maximum midexpiratory flow (MMEF) (−4.89%) and forced expiratory flow at 75% of expired FVC (FEF_{75}) (−6.62%), whereas in females these deficits were smaller (−1.93% and −2.45%, respectively) and were not statistically significant. However, larger deficits were seen in both males and females with longer time since diagnosis. In males with more than 6 yr since diagnosis, there were significant deficits in FEV_1 (−3.91%), MMEF (−7.39%), FEF_{75} (−8.12%), and peak expiratory flow rate (PEFR) (−4.65%) as compared with children with less than 3 yr since diagnosis. There were fewer females with more than 6 yr since diagnosis, but deficits were similar to those of males for FEV_1 (−2.52%), MMEF (−9.26%), and FEF_{75} (−14.28%). Large deficits in flow rates in both large and small airways were observed in males and females for whom asthma was reported to have been diagnosed before age 3 yr. There was little evidence that lung growth in children with asthma "catches up" at older ages. Therefore, because a constant percent deficit in lung function implies an increasingly large absolute deficit in older children with larger lungs, these results are consistent with prior evidence that lung function deficits in children with asthma persist into adulthood. We also suggest that in children, commonly observed differences between sexes in the impact of asthma on lung function may reflect differences in the duration and age of onset of asthma in males and females.

Asthma prevalence in the United States has been increasing at least since 1979 (1). Most of this increase has occurred among children under 18 yr of age, who constitute two-thirds of the 18-million Americans with asthma. Although it is well known that lung function is reduced during an asthma attack, the chronic effects of asthma on lung function have been examined in only a few prospective studies, which suggest that persistent deficits occur (2–8). Because the pattern of lung function growth varies and the occurrence of asthma differs in boys and girls of different ages, the persistent effect of asthma may vary in boys and girls. Two recent studies have reported conflicting results on sex differences in the effect of asthma on level of lung function (7, 8). In one of these studies, a larger percent deficit in FEV_1 was seen in males than in females with asthma (among children 6 to 18 yr of age who were examined annually between 1974 and 1989) (7). In contrast, longitudinal evaluation of an East Boston cohort found a deficit in FEV_1 only among females (8). Two potentially important factors in the natural history of asthma, duration and early age at onset (9, 10), were not explicitly examined in previous longitudinal studies of lung function, and may have accounted for these inconsistencies.

To investigate patterns of lung function in male and female asthmatic children, we evaluated the effect of time since diagnosis, age at diagnosis, and medication (inhaler) use among adolescent school children in a cohort participating in the Southern California Children's Health Study (11). The potential insight into the pattern of growth in pulmonary function (PF) among a population-based sample of asthmatic children as they approach adulthood is a major strength of this study. We used a flexible mixed-effects regression spline model to characterize the complex, nonlinear relationship of age, height, and PF with the age-related trend in lung function deficit associated with asthma.

METHODS

Study Design

The University of Southern California and California Air Resources Board Children's Health Study includes 12 communities within a 200-mile radius of Los Angeles. Details on the design, site selection, subject recruitment, and assessment of health effects in the study are reported elsewhere (12). Briefly, a total of 3,681 asthmatic and non-asthmatic children, approximately 50% of whom were fourth graders, 25% seventh graders, and 25% tenth graders, entered the study in early 1993. At baseline, a parent or guardian of each participating child provided written informed consent and completed a written questionnaire. This provided detailed information on demographics, history of respiratory illness and its associated risk factors, exposure information, and household characteristics. In the spring of 1993 and in each subsequent year, an update questionnaire was completed by each child, and PF testing was conducted. A telephone callback substudy was also conducted, in the summer of 1993, to determine the type and pattern of medication used by 205 asthmatic children. The research protocol for the study was approved by the Institutional Review Board of the University of Southern California. This report is limited to data from the first 4 yr of follow-up on the members of the fourth- and seventh-grade cohorts for whom there was adequate information on asthma characteristics. The data set for final analysis excluded 51 children for whom complete information on asthma was not available, and 20 children who had reported cystic fibrosis or severe chest injury before age 2 yr.

Pulmonary Function Data

PF testing was conducted on each participating child, at school, during the morning or early afternoon hours of the winter and spring months.

(*Received in original form January 31, 2000 and in revised form May 9, 2000*)

The statements and conclusions in this report are those of the contractor and not necessarily those of the California Air Resources Board. The mention of commercial products, their source or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products.

Supported by contract A033-186 from the California Air Resources Board, grants 5P30ES07048-04, 1P01ES0939581-01 from the National Institute of Environmental Health Sciences, contract CR824034-01-3 and grant R826708-01-0 from the Environmental Protection Agency, grant 1R01HL61768-01 from the National Heart, Lung, and Blood Institute, and the Hastings Foundation.

Correspondence and requests for reprints should be addressed to Kiros Berhane, Ph.D., Department of Preventive Medicine, USC Keck School of Medicine, 1540 Alcazar Street, CHP 220, Los Angeles, CA 90033. E-mail: kiros@rcf.usc.edu

Am J Respir Crit Care Med Vol 162. pp 1723–1730, 2000
Internet address: www.atsjournals.org

Each child was asked to perform up to seven maximum forced expiratory flow–volume maneuvers while breathing through a rolling-seal spirometer (Spiroflow; P.K. Morgan Ltd., Gillingham, UK), as previously described (11). Data were then extracted on FVC, FEV_1, maximum midexpiratory flow (MMEF), forced expiratory flow rate at 75% of expired FVC (FEF_{75}), and peak expiratory flow rate (PEFR). The calibrations of the six spirometers used in the study were checked just before, during, and after each day's testing session with flow–volume syringes (Jones Medical Instrument Co., Oak Brook, IL). Details of the quality control and data management procedures used have been previously reported (11).

Definitions of Asthma

A subject was defined as having asthma if a parent/guardian, in the baseline questionnaire, answered "yes" to the question "Has a doctor diagnosed your child with asthma?" or if the child answered "yes" to the question "Has a doctor ever said you had asthma?" during PF testing. The subjects were initially categorized into two groups, according to their asthma status at each PF testing period. The age at diagnosis of asthma was determined from the questionnaire for children who had physician-diagnosed asthma at baseline, and by designating the middle of the previous year as the age at diagnosis for those who reported physician-diagnosed asthma during follow-up. Duration of asthma, which was essentially the time since diagnosis, was calculated by subtracting age at diagnosis from age at the study visit for PF testing. Medication use for each year was assessed on the basis of a child's report of whether he or she used an inhaler for asthma. Asthmatic children were classified into subgroups based on age at diagnosis (with age categories of 0 to 2 yr, 3 to 5 yr, 6 to 9 yr, and 10 yr or more) and duration since diagnosis of asthma (with categories of 0 to 2 yr, 3 to 4 yr, 5 to 6 yr, and more than 6 yr), as described in the literature. To assess the combined effect of asthma duration and inhaler use, the asthmatic children were also classified into four mutually exclusive subgroups according to duration of asthma (low: $\leq$ 4 yr, and high: $>$ 4 yr) and medication (inhaler) use (yes/no).

Definitions of Smoking

Children who at any given visit reported smoking $>$ 100 cigarettes in their lifetime were classified as smokers. Environmental tobacco smoke (ETS) exposure was based on reports of current and past smoking status of each child's mother, father, other adult household members, and regular household visitors. Both of these binary variables were considered as potential confounders in the models used in the study.

Data Analysis

Descriptive statistics and sex-specific initial comparisons between subjects excluded or lost to follow-up and those included in the data analysis were made with respect to baseline characteristics via chi-square testing for association in contingency tables. Asthmatic children were compared through analysis of variance with nonasthmatic children with respect to physical and physiologic characteristics such as age, height, and weight.

The relationships between PF in children and physiologic measures such as age and height (HT) have been shown to be highly complex (7, 13). These relationships may not be adequately characterized by lin-

TABLE 1

BASELINE COMPARISONS OF THE SUBJECTS INCLUDED IN THE ANALYSIS, WITH TWO OR MORE PULMONARY FUNCTION MEASUREMENTS, AND THOSE WHO HAD NONE OR ONLY ONE PULMONARY FUNCTION MEASUREMENT

	Male			Female		
Baseline Characteristics	0–1 PFT (*n = 239*) n (%)	$\geq$ 2 PFT (*n = 1,172*) n (%)	p Value*	0–1 PFT (*n = 204*) n (%)	$\geq$ 2 PFT (*n = 1,105*) n (%)	p Value
Ethnicity						
Asian	8 (3.9)	63 (5.7)	$<$ 0.01	9 (3.8)	65 (5.6)	0.02
Black	19 (9.3)	51 (4.6)		22 (9.2)	62 (5.3)	
Hispanic	47 (23)	279 (25.3)		75 (31.4)	325 (27.7)	
Other	10 (4.9)	9 (0.8)		8 (3.4)	15 (1.3)	
White	120 (58.8)	703 (63.6)		125 (51)	705 (60.2)	
Grade						
4th	154 (75.5)	738 (66.8)	0.02	154 (64.4)	742 (63.3)	0.8
7th	50 (24.5)	367 (33.2)		85 (35.6)	430 (36.7)	
Asthma at entry						
Yes	24 (11.8)	166 (15)	0.9	16 (6.7)	105 (9)	0.8
No	133 (65.2)	894 (80.9)		170 (71.1)	997 (85)	
Missing	47 (23)	45 (4.1)		53 (22.2)	70 (6)	
Wheezing at entry						
Yes	64 (31.4)	384 (34.8)	0.5	55 (13)	340 (29)	0.08
No	125 (61.3)	667 (60.4)		165 (69)	772 (65.9)	
Missing	15 (7.4)	54 (4.9)		19 (8)	60 (5.1)	
Current wheeze†						
Yes	41 (20.1)	231 (20.9)	0.9	31 (13)	212 (18.1)	0.09
No	144 (70.6)	811 (73.4)		189 (79.1)	889 (75.9)	
Missing	19 (9.3)	63 (5.7)		19 (7.9)	71 (6.1)	
ETS exposure						
Yes	94 (46.1)	393 (35.6)	$<$ 0.01	129 (54)	423 (36.1)	$<$ 0.01
No	97 (47.5)	668 (60.5)		93 (38.9)	693 (59.1)	
Missing	13 (6.4)	44 (4)		17 (7.1)	56 (4.8)	
Insurance						
Yes	150 (73.5)	930 (84.2)	$<$ 0.01	169 (70.7)	952 (81.2)	$<$ 0.01
No	42 (20.6)	143 (12.9)		58 (24.3)	183 (15.6)	
Missing	12 (5.9)	32 (2.9)		12 (5)	37 (3.2)	

Definition of abbreviations: ETS = environmental tobacco smoke; PFT = pulmonary function testing.

* Chi-square tests for associations between baseline characteristics and completion of at least two PF measurements (did not include the missing category)

† Wheezing in previous 12 mo at time of entry.

earity or any other simple parametric form. Preliminary analysis of the data from the present study, and results of similar studies (13), have shown that although the relationship between log PF and log height (log HT) appears to be linear within short age intervals, the slopes and intercepts of this relationship tend to change with age. In order to properly account for dependence caused by repeated measurements made on the same child, and to capture the nonlinear and complex relationship between PF, age, and height, we fitted mixed-effects models that used spline terms for the age-dependent intercepts and slopes for height (14). All of the fitted models had the following general form:

$$E(\log[PF_{cij}]) = \mu + a_i + f_1(AGE_{cij}) + f_2(AGE_{cij}) \times \log(HT_{cij}) + X_{cij}\gamma + \alpha_g I_g + \beta_g I_g \times AGE_{cij}$$

where AGE is age, and c, i, j, and g denote the community, child, year of visit, and asthma group, respectively. In the foregoing model, a_i denotes a child-specific random intercept assumed to be normally distributed, with zero mean and finite variance σ^2_a; I_g denotes a dummy variable for the gth asthmatic group; and X_{cij} includes a set of potential confounders, including community, school grade, technician, spirometer, race/ethnicity, room temperature, barometric pressure, body mass index (BMI), respiratory infection at PF testing, and severe chest illness before age 2 yr. Exercising during the 30 min before PF testing, membership in a health insurance plan, personal smoking, and ETS exposure were also considered as potential confounders. The primary parameters of interest were the main effect (α_g) for an asthmatic group g, which characterizes a parallel percent deficit/gain in PF compared with the baseline PF of the group of nonasthmatic subjects (or other reference group), and the effect of the asthma × AGE term β_g, which reflects whether the percent deficit/gain in PF levels of asthmatic children varies with age. The child-specific random intercepts implicitly account for initial PF levels. Note that the models are additive on the logrithmic scale (and are hence multiplicative on the raw scale). Therefore, we give model results in terms of parallel percent differences ($[\exp(\alpha_g) - 1] \times 100$) from the reference curve at the mean age, and in terms of percent deviations ($[\exp(\beta_g) - 1] \times 100$) from parallelism. Analogous 95% confidence intervals are defined in a similar fashion.

All models were fitted separately by sex. The main effect of age (f_1), designed to show the age-specific intercepts of the log(PF) versus log(HT) relationship, and the slope of the log(HT) covariate (f_2), designed to show the age-specific slopes of the log(PF) versus log(HT) relationship, are given as unspecified smooth functions of age, and are estimated by using the adequately flexible and yet inherently parametric regression splines (15). The regression splines fit piecewise polynomials that are joined smoothly at the cutpoints, known as knots, and have the advantage of reducing to the well-established linear modeling framework once the number and position of the knots are determined. This has the advantage of allowing appropriate statistical inference while capturing the nonlinear relationships in the data (13). Initially, a knot was placed at each integral age. However, the final models were fitted by using knots at ages 12 and 14 yr for males and at ages 10, 12, 14, and 16 yr for females, leading to a more parsimonious model with essentially the same results.

Sex-specific models were fitted with the model just described, using white race/ethnicity and nonasthmatic subjects as the reference categories for race/ethnicity and asthma, respectively. Continuous covariates, such as room temperature, barometric pressure, and age were centered at their mean values. All analyses were done with the Splus statistical software package (Mathsoft Inc., Seattle, WA) (16).

RESULTS

The data set used for analysis consisted of 2,277 children (1,172 female and 1,105 male) who met the inclusion criteria. The 239 female and 204 male children from the original cohort who were excluded from the analysis because they did not have at least two PF testing visits were, irrespective of sex, more likely to be of black or Hispanic ethnicity, with greater ETS exposure and without health insurance (Table 1). The excluded females were also less likely to have reported wheezing at baseline, whereas the excluded males were more likely to come from the fourth-grade cohort. The ages at entry (in years) for the fourth- and seventh-grade cohorts were 10.1 ± 0.6 yr

TABLE 2

ASTHMA CHARACTERISTICS OF THE SUBJECTS WHO HAD AT LEAST TWO PULMONARY FUNCTION MEASUREMENTS

		Fourth-Grade		Seventh-Grade	
		Male	Female	Male	Female
Characteristics	Groups	n (%)	n (%)	n (%)	n (%)
Asthma status*	Asthmatic	166 (24.5)	123 (18.4)	78 (22.9)	77 (19.0)
	Nonasthmatic	512 (75.5)	547 (81.6)	262 (77.1)	328 (81.0)
	Total	678	670	340	405
Asthma duration,† yr	0–2	32 (20.7)	39 (34.8)	8 (11.6)	19 (26.0)
	3–4	38 (24.5)	27 (24.1)	7 (10.1)	16 (21.9)
	5–6	12 (7.7)	14 (12.5)	5 (7.2)	5 (6.8)
	> 6	73 (47.1)	32 (28.6)	49 (71.0)	33 (45.2)
	Missing	11	11	9	4
	Total	166	123	78	77
	Mean (SD)	5.3 (4.4)	4.1 (3.7)	8.1 (4.7)	5.5 (4.4)
	Median	3.5	2.6	7.5	3.7
Asthma duration and medication‡	Short duration, no medication	24 (17.9)	22 (23.2)	7 (10.9)	4 (6.5)
	Short duration, with medication	41 (30.6)	33 (34.7)	7 (10.9)	24 (38.7)
	Long duration, no medication	23 (17.2)	15 (15.8)	15 (23.4)	9 (14.5)
	Long duration, with medication	46 (34.3)	25 (26.3)	35 (54.8)	25 (40.3)
	Missing§	32	28	14	15
	Total	166	123	78	77

* Asthma status was determined at the end of the follow-up period.

† Time since diagnosis of asthma (at last visit). "Missing" represents children who said they were asthmatic but whose parents did not.

‡ Time since diagnosis of asthma at last follow-up visit (categorized as short (≤ 4 yr) or long (> 4 yr) by status of inhaler medication use at last follow-up visit).

§ Missing at last follow-up visit.

TABLE 3

SEX-SPECIFIC EFFECTS OF ASTHMA ON PULMONARY FUNCTION*

		Level (Asthma Main Effect)		Trend (Asthma × Age)	
Sex	PFT	Percent Difference	95 CI	Percent Difference	95 CI
Male					
	FVC	0.49	(−0.44, 1.44)	0.01	(−0.24, 0.27)
	FEV_1	−0.72	(−1.85, 0.42)	0.01	(−0.32, 0.34)
	MMEF	−4.89†	(−7.14, −2.59)	0.27	(−0.42, 0.96)
	FEF_{75}	−6.62†	(−9.65, −3.50)	0.56	(−0.40, 1.53)
	PEFR	−1.57	(−3.26, 0.14)	0.77†	(0.22, 1.33)
Female					
	FVC	0.81	(−0.14, 1.76)	−0.07	(−0.37, 0.24)
	FEV_1	0.19	(−1.02, 1.42)	−0.13	(−0.54, 0.28)
	MMEF	−1.93	(−4.41, 0.61)	−0.18	(−1.05, 0.69)
	FEF_{75}	−2.45	(−5.77, 0.10)	−0.1	(−1.19, 0.10)
	PEFR	−1.01	(−2.92, 0.93)	−0.34	(−1.03, 0.36)

Definition of abbreviations: CI = confidence interval; FEF_{75} = forced expiratory flow at 75% of FVC; MMEF = maximum midexpiratory flow; PEFR = peak expiratory flow rate; PFT = pulmonary function testing.

* All models are adjusted for age and height via flexible nonlinear terms. The models are also adjusted for community, technician, spirometer, group, ethnicity (white as baseline), respiratory infection at PFT, room temperature, barometric pressure, chest illness before age 2 yr and body mass index. Asthma effects are reported as comparisons with nonasthmatic subjects.

† $p < 0.01$.

(mean ± SD) and 13.1 ± 0.5 yr, respectively. The ranges in age (at entry) were 8.4 to 12.0 yr and 11.7 to 14.8 yr for the fourth- and seventh-grade cohorts, respectively.

Males in the two cohorts had a greater reported rate of physician-diagnosed asthma than did females, although the difference was smaller in the seventh-grade cohort (Table 2). The mean (and median) duration of asthma (in years) were longer in males. Asthmatic children, including those who had their disease diagnosed during the course of the study, appear to have had a similar pattern of participation in follow-up examinations to that of nonasthmatic children.

There was no difference between asthmatic and nonasthmatic children with respect to baseline age, height, and weight, with the exception that males who had asthma diagnosed during the course of the study were younger at baseline by approximate 4 mo (data not shown).

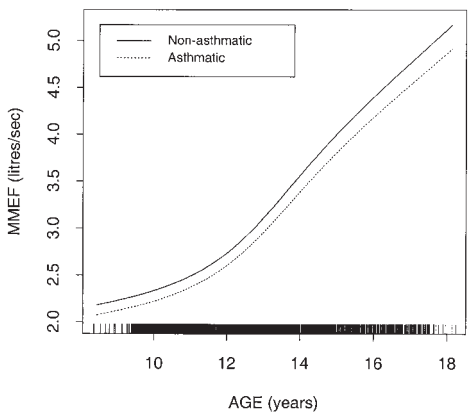

Figure 1. Growth curves of MMEF in male nonasthmatic (*solid line*) and asthmatic (*broken line*) children. The rugged plot at the bottom of the figure indicates the density of the data. The parallel shift between the two curves was found to be statistically significant ($p < 0.01$).

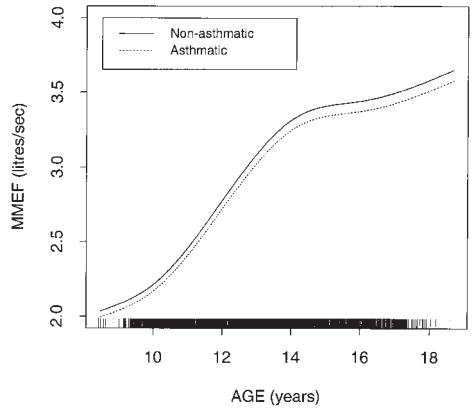

Figure 2. Growth curves of MMEF in female nonasthmatic (*solid line*) and asthmatic (*broken line*) children. The rugged plot at the bottom of the figure indicates the density of the data.

The results given by the initial sex-specific models that were fitted for all children to evaluate the overall effect of asthma on FVC, FEV_1, MMEF, FEF_{75}, and PEFR are summarized in Table 3. The greatest effects of asthma were seen in males. Males with asthma had a −4.89% deficit in MMEF ($p < 0.01$) and a −6.62% deficit in FEF_{75} ($p < 0.01$), with no significant trend toward improvement in these measures with increasing age (Table 3). The curves for MMEF with growth for males are given in Figure 1, in terms of absolute differences between nonasthmatic and asthmatic children, and show the deficit in asthmatic children. Of note is the greater absolute difference in MMEF at older ages, even though the percentage deficit remained the same. There was a −1.57% deficit for PEFR ($p = 0.07$), but there was also a significant trend toward improved PEFR levels (0.77% per year after 12.8 yr of age). This indicates that PEFR levels for males were improving and catching up to the level for nonasthmatic males. For females, the direction of the effects in the study measures was consistent with that for males, but none of the models showed any significant deficit. The MMEF

TABLE 4

EFFECTS OF DURATION OF ASTHMA AND RECENT MEDICATION USE ON PULMONARY FUNCTION OF ASTHMATIC MALES*

			Effects in Percent Differences				
Model	Covariate		FVC	FEV_1	MMEF	FEF_{75}	PEFR
1†	Duration‡, yr	3–4	−0.98	−1.31	−2.58	−3.59	−1.20
		5–6	−1.28‖	−2.55¶	6.81¶	−8.02‖	−3.54‖
		> 6	−2.34‖	−4.22¶	−7.94¶	−9.01‖	−4.42‖
2§	Short duration, with medication		1.28	0.93	−0.23	−0.80	−0.10
	Long duration, no medication		0.52	−0.60	−3.31	−3.66	−1.67
	Long duration, with medication		0.16	−2.11	−6.64‖	−7.77‖	−3.67‖

Definition of abbreviations: FEF_{75} = forced expiratory flow at 75% of FVC; MMEF = maximum midexpiratory flow; PEFR = peak expiratory flow rate.

* All models are adjusted for age and height via flexible nonlinear terms. The models are also adjusted for community, technician, spirometer, group, ethnicity (white as baseline), respiratory infection at pulmonary function testing, room temperature, and barometric pressure.

† Asthma effects are reported as comparisons with asthmatics with subjects with disease of 0–2 yr duration.

‡ Time since diagnosis, relative to 0 to 2 yr.

§ Asthma effects are reported as comparisons with asthmatic subjects with short duration of asthma and no recent medication use (short duration: ⩽ 4 yr, long duration: > 4 yr).

‖ $p < 0.05$.

¶ $p < 0.01$.

growth curves for nonasthmatic and asthmatic females, and their differences in absolute terms, are shown in Figure 2.

The potential effect of inhaler use and its interaction with duration of asthma were examined in models that included only asthmatic males (Table 4) and asthmatic females (Table 5). In asthmatic males, a significant deficit in the level of PF was associated with long duration of asthma (more than 4 yr) for all five pulmonary function measures examined in the study (Table 4). Moreover, the deficits were greatest for asthmatic males who had physician-diagnosed asthma for more than 4 yr and who used an inhaler (during the last year), for MMEF (-6.64%, $p < 0.05$), FEV_1 (-2.11%, $p = 0.13$), FEF_{75} (-7.77%, $p < 0.05$), and PEFR (-3.67%, $p < 0.05$) (Table 4).

In asthmatic females, longer duration of asthma (> 6 yr) was associated with a significant deficit ($p < 0.01$) in MMEF and FEF_{75} (-9.24% and -14.42%, respectively). These deficits, however, were more evident in children who had physician-diagnosed asthma for more than 4 yr and who reported using an inhaler for their asthma (Table 5). Our ability to examine the effect of longer duration of asthma and inhaler use in females was limited by the relatively few females who had asthma of long duration.

In the models that we used to examine the effect of inhaler use and duration of asthma (Tables 4 and 5), the reference group was the group with "short duration, no medication." In order to determine whether inhaler use was a good indicator of asthma activity, we examined its relationship with extensive information on asthma activity available at baseline and in the final year of the study. At baseline, 41% of the children in the short duration/no medication group reported wheezing during the previous 12 mo, probably suggesting bronchial hyperreactivity. However, 15.5% of the children in this group reported having "some" asthma in the previous 12 mo. At the last follow-up visit, 26% of the children in this group reported having symptoms such as chest tightness, coughing, or shortness of breath in the previous 12 mo.

At baseline, 65% of the children in the "long duration/no medication" group reported wheezing in the previous 12 mo, and 45% also reported having some asthma in the same period. At the last follow-up visit, 32% of the children in the long duration/no medication group reported having symptoms in

TABLE 5

EFFECTS OF DURATION OF ASTHMA AND RECENT MEDICATION USE ON PULMONARY FUNCTION OF ASTHMATIC FEMALES*

Model	Covariate		Effects in Percent Differences FVC	FEV_1	MMEF	FEF_{75}	PEFR
1†	Duration‡, yr	3–4	0.20	−1.11	−1.96	−3.23	−0.94
		5–6	0.05	−1.33	−4.42	−6.75	3.76
		> 6	−0.09	−2.49	−9.24‖	−14.42‖	0.76
2§	Short duration, with medication		−0.44	0.23	0.39	1.78	0.28
	Long duration, no medication		0.83	1.14	−0.77	−0.81	3.94
	Long duration, with medication		−0.71	−1.05	−5.45	−6.92	2.83

Definition of abbreviations: FEF_{75} = forced expiratory flow at 75% of FVC; MMEF = maximum midexpiratory flow; PEFR = peak expiratory flow rate.

* All models are adjusted for age and height via flexible nonlinear terms. The models are also adjusted for community, technician, spirometer, group, ethnicity (white as baseline), respiratory infection at pulmonary function testing, room temperature, and barometric pressure.

† Asthma effects are reported as comparisons with asthmatic subjects with asthma of 0 to 2 yr duration.

‡ Time since diagnosis, relative to 0 to 2 yr.

§ Asthma effects are reported as comparisons with asthmatic subjects with short duration of asthma and no recent medication use (short duration: ⩽ 4 yr, long duration: > 4 yr).

‖ $p < 0.05$.

TABLE 6

EFFECT OF ASTHMA ON PULMONARY FUNCTION BY AGE AT DIAGNOSIS FOR MALE SUBJECTS*

PFT	Asthma by Age at Diagnosis (yr)	Level (Asthma Main Effect) Percent Difference	95 CI	Trend (Asthma × Age) Percent Difference	95 CI
FVC	0–2	1.36	(−2.7, 5.6)	−0.17	(−0.8, 0.4)
	3–5	−1.14	(−5.5, 3.5)	0.51	(−0.2, 1.2)
	6–9	2.04	(−1.0, 5.1)	−0.61†	(−1.1, −0.1)
	⩾ 10	0.23	(−1.9, 2.5)	0.07	(−0.3, 0.4)
FEV_1	0–2	−4.98†	(−9.1, −0.7)	−0.03	(−0.8, 0.7)
	3–5	0.30	(−4.6, 5.4)	0.32	(−0.6, 1.3)
	6–9	−0.72	(−3.9, 2.6)	−9.6‡	(−1.6, −0.3)
	⩾ 10	−1.45	(−3.8, 1.0)	0.15	(−0.3, 0.6)
MMEF	0–2	−18.83‡	(−26.0, −11.0)	0.59	(−1.0, 2.2)
	3–5	4.33	(−5.9, 15.6)	−0.13	(−2.0, 1.8)
	6–9	−7.30†	(−13.4, −0.8)	−0.97	(−2.3, 0.4)
	⩾ 10	−6.49‡	(−11.0, −1.7)	−0.16	(−1.1, 0.8)
FEF_{75}	0–2	−23.77‡	(−32.7, −13.7)	0.26	(−2.0, 2.6)
	3–5	5.05	(−8.6, 20.7)	0.36	(−2.3, 3.1)
	6–9	−8.83†	(−16.8, −0.1)	−0.59	(−2.4, 1.3)
	⩾ 10	−6.91†	(−13.0, −0.4)	−0.07	(−1.4, 1.3)
PEFR	0–2	−6.47†	(−11.8, −0.8)	2.76‡	(1.4, 4.1)
	3–5	5.39	(−1.3, 12.5)	−1.85†	(−3.3, −0.4)
	6–9	−2.22	(−6.4, 2.1)	−1.38‡	(−2.4, −0.3)
	⩾ 10	−3.52†	(−6.5, −0.4)	0.44	(−0.3, 1.2)

Definition of abbreviations: CI = confidence interval; FEF_{75} = forced expiratory flow at 75% of FVC; MMEF = maximum midexpiratory flow; PEFR = peak expiratory flow rate; PFT = pulmonary function testing.

* All models are adjusted for age and height via flexible nonlinear terms. The models are also adjusted for community, technician, spirometer, group, ethnicity (white as baseline), respiratory infection at pulmonary function testing, room temperature, barometric pressure, chest illness before age 2 yr, and body mass index. Asthma effects are reported as comparisons with nonasthmatic subjects.

† $p < 0.05$.

‡ $p < 0.01$.

the previous 12 mo, such as chest tightness, coughing, or shortness of breath. Thus, the lack of inhaler use was not a good indicator that asthma was inactive.

In the groups that reported use of an inhaler for asthma, the number of children with disease activity was considerably higher than that of children who did not use an inhaler for asthma. At baseline, 85% of those who had asthma of short duration reported wheezing in the previous 12 mo, whereas 90% reported having some asthma. Similarly, 92% of children with asthma of long duration reported wheezing, whereas 94% reported having some asthma. These patterns also held at the last follow-up visit. Therefore, the reported use of an inhaler is a useful longitudinal indicator of disease activity.

A substudy of types and patterns of medication used for asthma found that 24% of children in the group with asthma of long duration with medication reported using both β-agonists and steroids, 6% used steroids only, and 55% used β-agonists only, whereas 15% used no medication at all. Thus, 70% of the children in this group used β-agonists only or used no medication at all.

Among male subjects, those who had asthma diagnosed before age 3 yr had significant deficits in their levels of MMEF (−18.83%, $p < 0.01$), FEV_1 (−4.98%, $p < 0.05$), FEF_{75} (−23.77%, $p < 0.01$), and PEFR (−6.47%, $p < 0.05$). Male children in whom asthma was diagnosed later (ages 6 yr and up) also showed significant deficits in MMEF and FEF_{75} (Table 6). These deficits were slightly greater for children who had asthma diagnosed when they were 6 to 9 yr old (−7.30% and −8.83% for MMEF and FEF_{75}, respectively) than for those who had asthma diagnosed when they were ⩾ 10 yr old (−6.49% and −6.91% for MMEF and FEF_{75}, respectively) (Table 6). The trend effect of asthma × AGE indicated that the deficit in children who had asthma diagnosed when they were 6 to 9 yr old increased with age at the approximate rate of −1%/yr, −0.6%/yr, and −1.4%/yr for FEV_1, FVC, and PEFR, respectively. The improvement in PEFR with age for males with asthma first diagnosed before age 3 yr (Table 6) appears to have been largely responsible for the time-dependent trend in PEFR "catching up" to that of males without asthma at older ages (Table 3). There was no indication of reversal of the deficits in levels of PF seen in males with asthma diagnosed when they were 0–2 yr old and ⩾ 6 yr old, with the exception of PEFR, for which there was a 2.76%/yr improvement (Table 6).

Asthmatic females who had asthma diagnosed before age 3 yr had a −15.66% ($p < 0.01$) deficit in their level of MMEF and a −22.82% ($p < 0.01$) deficit in their level of FEF_{75} (Table 7). Similarly, asthmatic females who had asthma diagnosed when they were ⩾ 10 yr old, in most of whom it was diagnosed during the follow-up years of the study, had significant deficits in all measures of PF except FVC (i.e., −5.67%, −2.47%, −6.75%, and −3.86% for MMEF, FEV_1, FEF_{75}, and PEFR, respectively) (Table 7). There was very little evidence of any greater percent deficit or improvement in PF at older ages (Table 7).

All of the models previously discussed were reanalyzed by adding smoking, ETS exposure, access to health care insurance, and exercising 30 min before PF testing as potential confounders. The effect of asthma on PF was found to be insensitive to the inclusion of these potential confounders (data not shown), and hence they were not included in the final models.

DISCUSSION

Duration of asthma from the time of its reported diagnosis was an important determinant of deficits in measures of both large and small airways function in males, and of deficits in small airways function (MMEF and FEF_{75}) in females. The shorter duration of asthma in females accounted for at least part of the observed difference between the overall effect of asthma in males and females. Confounding by town of residence, ethnicity, and other factors did not explain the results.

The effect of duration of asthma from its reported diagnosis has not been studied extensively in children, but the foregoing results are compatible with reported effects of duration of asthma on FEV_1 in selected children with asthma (9, 17). In the Childhood Asthma Management Program study of children with mild to moderate asthma, FEV_1 as a percent of the predicted value was lower if the duration of asthma was longer, although the effect of duration was greater in males (9). Longer duration of asthma may also result in more modest improvement in response to treatment with inhaled corticosteroids (17). Our results are not directly comparable with those of the population-based cohort study done by Gold and coworkers (7). However, among those children in our study with a longer time since the diagnosis of asthma, the effect was similar to the overall pattern of deficits reported by Gold and coworkers (showing significant effects of asthma on FEV_1, which were greater in males). Further study of the role of duration of asthma as a determinant of lung function is warranted, and might help clarify seemingly inconsistent reports of greater deficits in lung function in girls than in boys with asthma, as reported by Weiss and coworkers (8).

Among males with asthma of more than 4 yr duration, those reporting use of an inhaler for asthma in the previous year had almost twice the deficit in all flow rates of children not using an inhaler, an association with medication use that has also been noted by other investigators (7). A detrimental effect of medication is unlikely, and our results suggest that

TABLE 7

EFFECT OF ASTHMA ON PULMONARY FUNCTION BY AGE AT DIAGNOSIS FOR FEMALE SUBJECTS*

PFT	Asthma by Age at Diagnosis (*yr*)	Level (Asthma Main Effect)		Trend (Asthma × Age)	
		Percent Difference	95 CI	Percent Difference	95 CI
FVC	0–2	1.49	(−4.4, 7.7)	−0.07	(−1.0, 0.9)
	3–5	0.54	(−6.1, 7.7)	−0.59	(−1.7, 0.5)
	6–9	−0.60	(−4.2, 3.1)	0.27	(−0.3, 0.9)
	⩾ 10	−0.96	(−3.0, 1.1)	0.23	(−0.1, 0.6)
FEV_1	0–2	−3.34	(−9.2, 2.9)	−0.41	(−1.6, 0.8)
	3–5	−0.05	(−7.0, 7.4)	−0.46	(−1.9, 1.0)
	6–9	−1.61	(−5.3, 2.2)	0.41	(−0.4, 1.2)
	⩾ 10	−2.47†	(−4.6, −0.3)	0.11	(−0.3, 0.6)
MMEF	0–2	−15.66‡	(−25.6, 4.4)	−0.81	(−3.4, 1.8)
	3–5	−2.81	(15.8, 12.2)	−0.37	(−3.5, 2.8)
	6–9	−2.17	(−9.4, 5.7)	0.11	(−1.6, 1.8)
	⩾ 10	−5.67‡	(−9.7, −1.5)	−0.01	(−0.9, 0.9)
FEF_{75}	0–2	−22.82‡	(−34.8, −8.7)	−0.89	(−4.4, 2.7)
	3–5	−3.81	(20.7, 16.7)	−1.34	(−5.5, 3.0)
	6–9	−7.87	(−16.9, 2.2)	0.11	(−2.2, 2.4)
	⩾ 10	−6.75†	(−12.0, −1.1)	0.46	(−0.8, 1.8)
PEFR	0–2	−7.87	(−15.5, 0.4)	−1.57	(−3.6, 0.5)
	3–5	6.10	(−3.9, 17.2)	1.32	(−1.2, 3.9)
	6–9	2.45	(−2.8, 8.0)	1.14	(−0.2, 2.5)
	⩾ 10	−3.86†	(−6.7, −0.9)	−0.49	(−1.2, 0.3)

Definition of abbreviations: CI = confidence interval; FEF_{75} = forced expiratory flow at 75% of FVC; MMEF = maximum midexpiratory flow; PEFR = peak expiratory flow rate; PFT = pulmonary function testing.

* All models are adjusted for age and height via flexible nonlinear terms. The models are also adjusted for community, technician, spirometer, group, ethnicity (white as baseline), respiratory infection at pulmonary function testing, room temperature, barometric pressure, chest illness before age 2 yr, and body mass index. Asthma effects are reported as comparisons with nonasthmatic subjects.

† $p < 0.01$.

‡ $p < 0.05$.

this deficit reflected the more active disease observed in children requiring medication. Because many children in our study who were not using an inhaler (at baseline) actually had had recent disease activity, the real deficits in lung function associated with recent disease activity may have been even larger than those observed for inhaler users versus nonusers.

There were large deficits in levels of PF among males with asthma of more than 4 yr duration since diagnosis, even if they did not require use of an inhaler (Table 4). As compared with males without asthma, these deficits were significant for all lung function measures, except FVC and PEFR (results not tabulated). These results are consistent with the finding of persistent deficits in flow rates that were not responsive to bronchodilators (6). Airway remodeling resulting from persistent inflammation has been demonstrated in both the experimental and clinical setting, and is a plausible mechanism for irreversible deficits in flow rates associated with asthma (18, 19). However, because many of the children in our study who were not using an inhaler had recent disease activity (at baseline), it is also possible that the deficits associated with asthma of long duration without medication were a result of untreated reversible bronchospasm, rather than being fixed deficits caused by airway remodeling. It is remarkable that so few of the children receiving treatment were receiving inhaled steroids, suggesting that undertreatment of asthma may have been an important contributor to the deficits observed in our study.

The impact of asthma on lung function in adolescence was most pronounced among children in whom asthma was diagnosed before age 3 yr, a group with mean flow rates in small airways that were only about 80% of those in children without asthma. In a cohort of children followed from birth, Martinez and associates observed that children with wheezing illness before age 3 yr had lower levels of PF at age 6 yr, whether they had asthma or not (10). However, it is unlikely that the children in our study with early diagnoses of asthma were misdiagnosed cases of transient early wheezing, because 79% of the males and 92% of the females in this group reported continued wheezing at age 6 yr, and more than half of the males and two-thirds of the females reported wheezing during the year before their initial interview in the fourth or seventh grade. These results are consistent with those of a study of Australian school children, which found that most of those who had severe asthma at age 14 yr, and concomitant significant deficits in FEV_1, had had their asthma diagnosed before age 3 yr (20). Among children followed into adulthood, FEV_1 and FEV_1/FVC were reduced to a greater extent in those with asthma onset at an early age (6). However, as in our study, recall of age of diagnosis, assessed retrospectively in these studies, may have been biased, and may have resulted in parents preferentially remembering particularly severe initial presentations of asthma at an early age or being more likely to report an earlier age at onset for particularly severe asthma that in fact first occurred at a somewhat older age. However, in our study, recent wheezing at the time of completion of the baseline questionnaire was no more frequent among children with a reported diagnosis of asthma before age 3 yr than among those with diagnosis at a later age.

On the log scale, there were no remarkable age-related trends in lung function that suggested improving or deteriorating lung function, with the exception of a significant deterioration in later years both in lung volume and flow rates in males with asthma diagnosed between ages 6 and 9 yr, and an opposite trend in PEFR in males, depending on the age of diagnosis. A similar pattern to that observed in the group with asthma diagnosed between ages 6 and 9 yr was observed in the Australian cohort, in which a large FVC in childhood declined to normal by age 21 yr (5). We have no explanation for the anomalous trends in PEFR. However, these age-related trends in lung function, which vary by age at diagnosis and are apparent only in boys, warrant further investigation.

Limitations to our study included the self reporting of physician-diagnosed asthma, which was not validated directly against physician records, bronchial hyperreactivity, or some similar objective measurement. Therefore, it was not possible to independently verify the relatively high cumulative report of a diagnosis of asthma at any time since birth (20.4% to 24.4%, depending on grade and sex; Table 2). To the extent that asthma may have been overreported, our results may have underestimated the effect of true asthma on PF. However, we used a standard definition for asthma, based on a standardized questionnaire used widely in epidemiologic studies in the United States. Our results can therefore be generalized to other populations in the United States (21). In addition, self reporting has been found to reflect what physicians actually report to patients, at least among adults (22, 23), and physician assessment of asthma has been recommended as the "gold standard" for this disease, for which a more precise diagnosis is not available (24). Differential loss to follow-up among asthmatic children in our study, especially if it occurred according to severity of illness and age at diagnosis, might have biased the observed estimates of effects of asthma on PF, and especially the estimates of age-related trends. However, children with both prevalent and newly diagnosed asthma appear to have had patterns of participation in follow-up examinations that were similar to those of children without asthma (Table 1). Another limitation of the study was the lack of complete longitudinal information that would have made it possible to evaluate the modulating effect of different types of medication on lung function deficits.

The generally constant percent deficit in lung function in the group of asthmatic children in our study as they approach adulthood implies an increasing absolute deficit in lung function in older asthmatic children because older children have larger lungs. According to our results, for example, a male with a −4.89% deficit (Table 3) in MMEF at age 10.1 yr (the mean age of our fourth-grade cohort at entry) and an average height (140.3 cm) would have had an absolute deficit in MMEF of −113.5 ml, but by 15 yr of age (average height: 170.2 cm), this deficit would be −187.2 ml for the same −4.89% deficit in MMEF. The lack of recovery of deficits with age, at least for small airways, adds to the evidence from the few studies that have followed asthmatic children into adulthood suggesting that deficits persist, at least among some subgroups (2–4, 25, 26). In the Netherlands and in Scotland, FEV_1 among asthmatic children was predictive of adult FEV_1 (3, 4, 26). Australian children who subsequently reported frequent wheezing at age 28 yr had an accelerated decline in respiratory function (2). Among British children followed from 0 to 35 yr of age, those with asthma of early onset and persistent wheezing had significant reductions in FEV_1 and FEV_1/FVC in adulthood, which were only partly reversible by β-agonists (25). Clinical studies demonstrating airway remodeling as a result of persistent inflammatory effects of undertreated asthma identify a possible underlying pathophysiologic basis for these deficits, and are the basis for chronic treatment designed to reduce such persistent deficits (27, 28).

As affected children reach adulthood and old age, the probable consequences of the current epidemic of childhood asthma in the United States are unknown. However, the deficit associated with persistence of asthma into adulthood has been reported to be greater than that associated with smoking (6). Among adults with asthma, there is evidence that on ac-

celerated decline in FEV_1 occurs with age (29, 30). Moreover, although the relationship between asthma and chronic airway obstruction is not altogether clear, deficits in FEV_1 in adults with chronic airways obstruction are predictive of mortality (31, 32). Better understanding of the pattern of lung growth and morbidity associated with asthma throughout life might help guide and evaluate treatment strategies designed to reduce the morbidity associated with this disease.

***Acknowledgment*:** The authors are grateful for the advice and thoughtful comments of David Bates, Jonathan Samet, and Frank Speizer, and for the input to this study, from the rest of our External Advisory Committee, composed of Morton Lippmann, John Spengler, James Whittenberger, Arthur Winer, and Scott Zeger. They acknowledge the hard work of the study field team and the cooperation of the 12 participating communities, the school principals, the many teachers, the students, and their parents. Programming support was provided by Jun Manila. Editorial support was provided by Ann Harris.

References

1. Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E, Kang DS. Surveillance for asthma—United States, 1960–1995. *MMWR CDC Surveill Summ* 1998;47:1–27.
2. Kelly WJ, Hudson I, Raven J, Phelan PD, Pain MC, Olinsky A. Childhood asthma and adult lung function. *Am Rev Respir Dis* 1988;138: 26–30.
3. Roorda RJ, Gerritsen J, van Aalderen WM, Schouten JP, Veltman JC, Weiss ST, Knol K. Follow-up of asthma from childhood to adulthood: influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol* 1994;93:575–584.
4. Godden DJ, Ross S, Abdalla M, McMurray D, Douglas A, Oldman D, Friend JA, Legge JS, Douglas JG. Outcome of wheeze in childhood: symptoms and pulmonary function 25 years later. *Am J Respir Crit Care Med* 1994;149:106–112.
5. Martin AJ, Landau LI, Phelan PD. Lung function in young adults who had asthma in childhood. *Am Rev Respir Dis* 1980;122:609–616.
6. Strachan DP, Griffiths JM, Johnston ID, Anderson HR. Ventilatory function in British adults after asthma or wheezing illness at ages 0–35. *Am J Respir Crit Care Med* 1996;154:1629–1635.
7. Gold DR, Wypij D, Wang X, Speizer FE, Pugh M, Ware JH, Ferris BG Jr, Dockery DW. Gender- and race-specific effects of asthma and wheeze on level and growth of lung function in children in six U.S. cities. *Am J Respir Crit Care Med* 1994;149:1198–1208.
8. Weiss ST, Tosteson TD, Segal MR, Tager IB, Redline S, Speizer FE. Effects of asthma on pulmonary function in children: a longitudinal population-based study. *Am Rev Respir Dis* 1992;145:58–64.
9. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP) [see comments]. *J Allergy Clin Immunol* 1999;103:376–387.
10. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: the Group Health Medical Associates [see comments]. *N Engl J Med* 1995;332:133–138.
11. Peters JM, Avol E, Gauderman WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong H Jr, *et al.* A study of twelve Southern California communities with differing levels and types of air pollution: II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999;159:768–775.
12. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H, *et al.* A study of twelve Southern California communities with differing levels and types of air pollution: I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med* 1999;159:760–767.
13. Wypij D, Pugh M, Ware JH. Modeling pulmonary function growth with regression splines. *Statist Sinica* 1993;3:329–350.
14. Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. New York: Oxford University Press; 1994.
15. Hastie TJ, Tibshiarni RJ. Generalized additive models. London: Chapman and Hall; 1990.
16. Becker RA, Chambers JM, Wilks AR. The new S language. Pacific Grove, CA: Wadsworth and Brooks/Cole; 1988.
17. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–381.
18. Paganin F, Seneterre E, Chanez P, Daures JP, Bruel JM, Michel FB, Bousquet J. Computed tomography of the lungs in asthma: influence of disease severity and etiology. *Am J Respir Crit Care Med* 1996;153: 110–114.
19. Wilson JW. What causes airway remodelling in asthma? *Clin Exp Allergy* 1998;28:534–536.
20. McNicol KN, Williams HB. Spectrum of asthma in children: I. Clinical and physiological components. *Br Med J* 1973;4:7–11.
21. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1–120.
22. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J* 1989;2:940–945.
23. Greer JR, Abbey DE, Burchette RJ. Asthma related to occupational and ambient air pollutants in nonsmokers. *J Occup Med* 1993;35:909–915.
24. Burr ML. Diagnosing asthma by questionnaire in epidemiological surveys [editorial]. *Clin Exp Allergy* 1992;22:509–510.
25. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195–1199.
26. Shaheen SO, Sterne JA, Florey CD. Birth weight, childhood lower respiratory tract infection, and adult lung function. *Thorax* 1998;53:549–553.
27. Merkus PJ, Borsboom GJ, Van Pelt W, Schrader PC, Van Houwelingen HC, Kerrebijn KF, Quanjer PH. Growth of airways and air spaces in teenagers is related to sex but not to symptoms. *J Appl Physiol* 1993; 75:2045–2053.
28. CAMP corporate paper. The Childhood Asthma Management Program (CAMP): design, rationale, methods. Childhood Asthma Management Program Research Group. *Control Clin Trials* 1999;20:91–120.
29. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194–1200.
30. Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987;70:171–179.
31. Schunermann HJ, Dorn J, Grant BJB, Winkelstein W, Trevisan M. Is pulmonary function a long-term predictor of mortality in the general population? [abstract]. *Am J Respir Crit Care Med* 1999;159:A320.
32. Peto R, Speizer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM, Higgins ITT, Gray RG, Richards SM, Gilliland J, Norman-Smith B. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. *Am Rev Respir Dis* 1983;128:491–500.